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Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

September 13, 1999

Docket # 99N-0193

Gentlemen:

Attached are two copies of the National Pharmaceutical Alliance's Technical Committee comments on the proposed rule on Supplements and Other Changes to an Approved Application. The latter was published in the Federal Register June 28, 1999, Vol. 64, No. 123. Today is the closing date for comments. We appreciate the opportunity to comment.

Very truly yours,

Robert A. Jensen for

Christina Sizemore
President

99N-0193

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COMMENTS FORM NPA'S TECHNICAL COMMITTEE ON THE PROPOSED REGULATION §314.3, §314.50, §314.60 and §314.70; Docket # 99N-0193

General Comments:

1. §314.70(b)(1) describes changes that require prior approval of a supplement and wisely uses the language from FDAMA Section 506A(c)(2) where a major change is one that has a *"substantial potential* to adversely affect the identity, strength, quality, purity, or potency of the drug as they relate to the safety or effectiveness of the drug." However, in proposed §314.70(b)(1)(iii), (iv), and (vi) the term "may affect" is used to describe three changes that require prior approval. There is a great difference between "substantial potential" and "may affect". The latter is a much weaker term indicating possibility (also permission or contingency). One could argue that everything is possible but that "may affect" doesn't seem to correlate with a major change which has "substantial potential". If FDA really believes that these three changes, namely, in the manufacture of a drug substance, changes to the container/closure system, or changes affecting sterility assurance are in the class of "may affect", then it must not believe these to be major changes. This is particularly true for changes that may affect sterility assurance since any change may affect one or more attributes of a sterile drug. We recommend that the changes discussed be placed outside of the major class or that FDA reevaluate them to determine if the agency really considers them major and if it concludes that they are, uses more appropriate wording in the regulation.

The above recommendation is made because the draft guidance "Changes to an Approved NDA or ANDA" lists a number of changes to sterile products or sterile product manufacture, any one of which *may* affect sterility assurance, but not all of which require pre-approval supplements. In order to require a pre-approval supplement the change should have a high probability (substantial potential) of affecting sterility assurance or, if not, it should be a CBE or AR report reporting mechanism.

2. The proposed regulation has an overwhelming emphasis on post approval changes for drug products and little on drug substances. The document is written for the sponsor of a drug application but has nothing in it for the DMF holder. We recommend that the latter be addressed.

3. Unfortunately, the classification system used depends on the "potential" of a change to have an impact. This may usually work in the drug product area but is less apt to for the drug substance where the actual change may only be gauged by the data obtained when the change is made. Perhaps a different rating system should be used for drug substances?

4. Last but not least the regulation doesn't appear to give the amount and kind of regulatory relief which seems to be embodied in FDAMA.

Specific Comments:

1. §314.3 contains a definition which didn't seem to be needed previously, that is, "specifications and test procedures" which appears in present Section 314.50 and has for years is now replaced with the word "specification" and now the latter means both tests and specifications. This one word to represent several things is confusing and the old section 314.50 is better, contains more meaning and everyone knows it.

Also a definition is given for a word which is inherently confusing since "validate" has had a meaning for a long time in the industry. Instead of "Validate the effects of the change", the phrase "Assess the effects of a change" should be used and validate left to its old historic meaning.

2. §314.70(a)(2) states that "The holder of an approved application under section 505 of the act shall validate the effects of the change ----------." The word validate should be eliminated from this section lest it be confused with the idea of validation in analytical and GMP terms where it is used in this proposed regulation for manufacturing changes. The word "assess" is a better one to use.

3. Current §314.70(c)(3) allows a different facility to be used for the production of the drug substance under certain conditions. FDA proposes not to include these changes in this proposed rule but intends to provide recommendations in certain guidance documents.

This section in the present regulations should be left in the revised regulations since the industry is familiar with this section of the regulations and has used it for years. We further propose that the phrase in the current regulation "covering that manufacturing process" be deleted.

4. §314.70(c)(5)(ii) states that during the 30-day period following receipt of the supplement, FDA will perform a preliminary review to see if it's complete and whether the type of change is appropriate under §314.70(c). If FDA determines that the change is properly submitted but the required information is incomplete, the applicant will be required to supply the missing information and wait until FDA determines that the supplement is in compliance before distributing the product.

The term "in compliance" is taken to mean that the information package within the supplement is complete. However, when FDA determines that the information is incomplete, why must a firm wait for both its submission of that necessary information for completeness *and* for FDA's determination before the firm may market the product? After all, this is only a preliminary review, not a full review which may indicate some deficiencies in the data. As long as the firm submits the data, it should be able to go to market and not wait until FDA determines that the supplement is "in compliance" which could take months since FDA is not now bound by the 30 day requirement.

5. §314.70(c)(6) allows certain changes to be placed into effect before a 30 day waiting period. One of these would be a change in the size and/or shape of a container for nonsterile drug products, except for solid dosage forms, but containing the same amount of product.

Why must the amount of drug product remain the same? If one changed a 125 mL container that held 100 mL of a liquid drug to a 250 mL container still containing 100 mL of drug product wouldn't the container size to drug ratio be the same as obtained by reducing the contents from 100 mL to 50 mL and leaving the container size at 125 mL? The former would be allowed but the latter would not?

6. Proposed §314.70 (c)(6)(i) as changes being effected for the addition of a specification or changes in the methods or controls to "provide increased assurance" that the drug will have the characteristics that it purports or is represented to possess. We recommend that this section be moved to §314.70(d) minor changes to be described in an annual report since they will not have a moderate potential to have an adverse effect on the drug product since by using the phrase "provide increased assurance", FDA is essentially classifying the change as minor.

7. §314.70(c)(7) proposes that if FDA disapproves a supplemental application under this section, the agency may order the manufacturer to cease distribution of the drug products made with the manufacturing change. Although this is the language contained in Sec. 506A(d)(3)(B)(iii) of FDAMA, it is a reversal of the long-time FDA policy of allowing firms to respond to deficiencies and get the supplement approved without interfering with distribution. Our recommendation is that FDA continue its long standing policy.

8. §314.70(d)(2)(i) relates to changes that may be reported in an annual report. One such change is any change to comply with an official compendium "that is consistent with FDA requirements and provides increased assurance that the drug will have the characteristics of identity, strength, quality, purity or potency". The quoted phrase does not exist in the current §314.70(d)(1) and is an escalation of the current requirements. This has occurred because FDA now considers that all compendial changes do not provide "increased assurance" that the drug will have the characteristics that it purports to have. But why must a compendial change provide increased assurance? Perhaps it provides the same assurance as previously even though a test is dropped. For instance, dropping a selenium test from a Δ 1,4 diene-3-keto steroid USP monograph was done when selenium dioxide was no longer used in the dehydrogenation of the steroid A ring. The latter had no impact on the characteristics of the steroids, it just dropped a useless test.

FDA is involved in the USP revision process and thus should be in on changes to monographs and not use regulations to preempt normal pharmacopeial changes. The wording of this section should remain as in the current regulations i.e."any change".

The same wording re USP changes appears for biologics in §601.12(d)(2)(i) for which the same recommendation is made.

September 13, 1999